

SUMMARY BASIS FOR APPROVAL

PLA#: 951210
ELA# 951190

Manufacturer: Centocor, B. V.
Einsteinweg 101
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The Netherlands

Licensed Name: Imciromab Pentetate

Trade Name: Myoscint™

Common name: R11D10

Date of Approval: July 3, 1996

Imciromab Pentetate is a Fab fragment of a murine IgG_{2b} anti-myosin bound to DTPA that may be radiolabeled with indium for imaging of irreversibly injured heart muscle. Anti-myosins react only with muscle cells whose membrane integrity has been damaged, since myosin is expressed exclusively in the intracellular compartment. This concept forms the basis of the antibody's capacity to image infarcted heart tissue.

I. INDICATION FOR USE

Indium In 111 MYOSCINT is a cardiac imaging agent for detecting the presence and location of myocardial injury in patients with suspected myocardial infarction.

II. DOSAGE FORM, ROUTE OF ADMINISTRATION, AND RECOMMENDED DOSAGE

The recommended intravenous dose of Indium In 111 Imciromab Pentetate is 2 mCi (74 MBq) with a range of 1.8 to 2.2 mCi (67 to 81 MBq). The activity of each dose should be measured by a suitable radiation calibration system just prior to administration. Indium In 111 Imciromab Pentetate is administered as an intravenous bolus over less than one minute.

The recommended imaging time is approximately 48 hours after intravenous injection. Within the first 24 hours after administration, clearance of radioactivity from the blood pool may not be sufficient for image interpretation. Imaging is performed with a gamma scintillation camera equipped with at least 37 photo multiplier tubes, a medium energy collimator optimized for Indium In 111 photons, and if possible, a sodium iodide crystal at least 3/8 inch (9.5 mm) in thickness. Typically, anterior, approximately 45° anterior oblique, and left lateral (or steep left anterior oblique) views of the chest are obtained for at least 10 minutes per view.

III. MANUFACTURING AND CONTROLS

A. Manufacturing

The monoclonal antibody is produced by standard hybridoma technology. The immunogen used was purified and well-characterized human cardiac myosin. The immunization of mice preceded fusion with the

myeloma cell line, Screening by radioimmunoassay (RIA) on human cardiac myosin yielded reactive clones. The hybridoma cell line used in manufacture of this product

(b)(4)

All of the cell banks (MCB, MWCB) have been tested for microbial and viral contaminants in accordance with the United States Food and Drug Administration (FDA) *Points to Consider in the Characterization of Cell Lines Used to Produce Biologicals* (1993) and *Draft Points to Consider in the Manufacture and Testing of Monoclonal Antibody Products for Human Use* (7994). The cell banks are free of microbial contaminants, adventitious murine viruses and bovine viruses, and adventitious viruses other than retroviruses.

Raw materials and packaging components intended for use in the production of Imciromab and the finished dosage form Imciromab Pentetate, are subjected to appropriate quality control evaluations before they are used in manufacture.

In process controls (Appendix A) and specifications for final bulk product (sterility, pH, protein identity [immunoelectrophoresis, IEF], In-111 incorporation by ITLC) have been routinely met (Appendix B). Final bulk may be stored for up to 14 days at 2-8° C prior to filling. Final container testing has also demonstrated consistency of manufacture (Appendix C). Potency of the product is determined by immunoaffinity chromatography on canine heart myosin and always exceeds 94% of maximal expected incorporation.

Extensive biochemical characterization includes mass spectroscopy, amino acid analysis, tryptic mapping, monosaccharide analysis and circular dichroism spectra, in addition to standard biochemical analyses for QA and QC. Imciromab Pentetate binds exclusively to heart and skeletal muscle myosin *in vitro*.

DTPA is covalently bound to Imciromab and purified by gel-filtration chromatography, permitting radiolabeling of the conjugate (Imciromab Pentetate) with Indium In 111 using Indium In 111 chloride. The Imciromab Pentetate kit is comprised of two vials, each containing a sterile, non-pyrogenic clear, colorless solution. The Imciromab Pentetate vial contains 0.5 mg of Imciromab Pentetate in 1.0 mL of 10 mM sodium phosphate buffer, 145 mM sodium chloride and 10% (w/v) maltose (pH 6.5) with no preservatives. One (1.0) mL of the solution from the Imciromab Pentetate vial is to be added to the Citrate buffer vial, which contains 1.0 mL of 0.2 M sodium citrate buffer solution (pH 5.0). Imciromab Pentetate is to be radiolabeled by the addition of a sterile, non-pyrogenic solution of high purity Indium In 111 Chloride from Mallinckrodt Medical.

B. Validation

Process validation studies were performed to demonstrate that the Imciromab manufacturing process yields a product meeting its predetermined specifications and quality attributes (Appendix D). These studies include validation of fermentation, downstream processing, virus removal and/or inactivation (removal of model viruses [MuLV, > 15 logs; SV-40, >10 logs; Polio, >6 logs] by protein A chromatography steps (2), anion exchange and gel-filtration chromatography, papain digestion and DTPA coupling reactions) and

product consistency. The purification process was also validated for the removal of various low molecular weight contaminants and reagents (Appendix E).

C. Stability Studies

Stability of Imciromab and Imciromab Pentetate has been demonstrated by chemical, physical and immunological tests (radioactivity incorporation, IEF, particle formation, immunoreactivity most relevant). Tests were done at elevated (22°C and 35°C), sub-ambient (-20°C), and recommended (2-8°C) storage temperatures. These tests indicated that harvests are stable at 2-8°C for two weeks, concentrates may be stored at 2-8°C for up to 9 weeks, downstream processing intermediates may be stored for fewer than 3 days at 2-8°C, the final bulk may be stored for up to 14 days at 2-8°C, and the final diluted preparation is stable for at least 18 months at 2-8°C.

D. Labeling

The labeling, including container label cartons and package insert (exhibit 1) have been reviewed for compliance with 21 CFR 201.6, 201.57, 610.60, 610.61 and 610.62. The trade name, MYOSCINT, is not known to be in conflict with that of any other approved product.

E. Establishment Inspection

A prelicensing inspection of Centocor's production facilities in Leiden, the Netherlands, was conducted by the Center for Biologics Evaluation and Research on April 15-18, 1996. Facilities and procedures were found to be in compliance with current Good Manufacturing Practices. Responses to Form FDA 483 were submitted by Centocor on May 21, 1996. On June 26, 1996 Centocor submitted its intent to complete, within six months of approval, all action items from this response.

F. Environmental Impact Analysis Report (EIAR)

An Environmental Impact Analysis Report was submitted by Centocor, Inc. as part of the establishment and product license applications. All applicable national and local environmental regulations are observed.

IV. PHARMACOLOGY

A. Pharmacokinetics

In humans, blood concentration-time curves of Indium In 111 Imciromab Pentetate were fit to a two-compartment model. The initial (α) elimination half-life of Indium In 111 Imciromab Pentetate radioactivity is 1.5 hours, while the slow (β) elimination half-life is 20.2 hours. At 24 hours, 19.2% of the initial radioactivity remains in the plasma, compared with 8.4% remaining at 48 hours. The elimination half-lives of Imciromab Pentetate as determined by enzyme-linked immunosorbent assay or by measuring radioactivity are not significantly different. The pharmacokinetics of Indium In 111 Imciromab Pentetate have not been evaluated in patients with hepatic, renal, or cardiac insufficiency.

B. Pharmacodynamics

Intravenous administration of Imciromab Pentetate radiolabeled with Indium In 111, a gamma emitting radionuclide, provides a means of identifying regions of myocardial infarction (MI) using scintigraphic techniques. In normal myocardium, intracellular proteins are isolated from the extravascular space by the cell membrane and are inaccessible to antibody binding. Cardiac myosin was chosen as the intracellular target for antibody localization because of its abundance in myocytes, its high molecular weight (500,000 Daltons), and its low plasma solubility. Heavy chain myosin is not found free in the circulation. Imciromab

Pentetate contains the Fab fragment of the antibody rather than the whole immunoglobulin because the smaller Fab fragment localizes to the injured myocardium to a greater degree and is cleared more rapidly from the circulation.

Circulating radiolabeled Imciromab Pentetate does not have access to intracellular myosin *in situ* and does not localize in normal myocardial tissue. Following myocyte injury, the cell membrane undergoes a loss of integrity and becomes permeable to macromolecules, allowing Indium In 111 Imciromab Pentetate to bind to intracellular myosin. Cross-reactivity studies performed *in vitro* on a broad spectrum of human tissues demonstrated that Imciromab Pentetate is highly specific for myocardial and skeletal muscle and does not cross-react with any of the other examined tissues.

In vivo, radiolabeled Imciromab Pentetate localizes in infarcted myocardial tissues. In healthy volunteers, cardiac images did not show Indium In 111 Imciromab Pentetate localization in the myocardium. Post-mortem evaluations of patients who died from complications of acute myocardial infarction shortly after Indium In 111 Imciromab Pentetate imaging demonstrated localization of Indium In 111 Imciromab Pentetate in the necrotic myocardium. The locations of the ante-mortem and post-mortem Indium In 111 Imciromab Pentetate myocardial uptake correlated with the location of the histochemically-determined myocardial infarct.

C. Toxicology

Single or multiple dose toxicity studies in dogs, rats, and non-human primates failed to reveal significant clinical, biochemical, or pathological abnormalities.

V. CLINICAL EXPERIENCE

A. Overview of Clinical Studies

In support of the proposed indication, the sponsor submitted ten clinical study reports and numerous reprints from the medical literature. Of the ten clinical study reports, seven describe the use of Imciromab Pentetate in the setting of ischemic heart disease. This included the phase 3 trial which examined the use of Imciromab Pentetate in patients with suspected acute myocardial infarction (Protocol C04I-001/C04I-002). The remaining three reports described the use of Imciromab Pentetate in other settings (i.e., blunt chest trauma, AIDS, and doxorubicin toxicity). Overall, a total of 1,329 subjects were studied in the clinical trials. 1,287 of these subjects were included in the assessment of the use of Imciromab Pentetate in ischemic heart disease. The most pertinent clinical data supporting the safety and efficacy of Imciromab Pentetate were obtained from the phase 3 study (Study C04I-001/C04I-002) and a supportive study (Study C04I-005). In the phase 3 study the diagnostic accuracy of Imciromab Pentetate imaging in acute myocardial infarction was assessed. In the supportive clinical study the diagnostic accuracy of Imciromab Pentetate was assessed in the diagnosis of myocardial infarction when Imciromab Pentetate injection and imaging were performed at various delayed time intervals following the acute myocardial infarction.

B. Study C04I-001/C04I-002: Multicenter clinical trial of the safety and diagnostic accuracy of Indium In 111 labeled antimyosin for detecting myocardial necrosis in ischemic heart disease

The phase 3 study was conducted in 1987 and 1988. An independent audit of the clinical data, commissioned by the sponsor, verified the reliability of the source clinical data, but recommended that the data be submitted to a reanalysis. These source data and reanalysis results provided the most detailed assessment of the safety and efficacy for Imciromab Pentetate.

The phase 3 study was a single-arm, non-randomized clinical trial performed at multiple clinical centers in patients hospitalized with chest pain considered by the investigator to be due to an acute myocardial infarction. Patients were to be injected with Imciromab Pentetate within 48 hours of the onset of chest pain. Planar and tomographic images were to be performed at 24 and 48 hours following Imciromab Pentetate injection. In the reanalysis of the source data, patients were assigned clinical diagnoses (i.e., acute myocardial infarction, unstable angina, chest pain of other etiology, nondefinitive) by a team of cardiologists blinded to the results of Imciromab Pentetate imaging. Another team of imaging physicians interpreted the cardiac images using a consensus approach but without knowledge of the clinical history and outcome. These data were used to generate the sensitivity, specificity, and likelihood ratios for Imciromab Pentetate imaging in the setting of acute ischemic heart disease.

Results

The study was conducted at 16 USA clinical centers and nine European centers. Overall, 730 Imciromab Pentetate injections were given to a total of 726 patients (four patients received two injections).

Of the 726 enrolled patients, 555 patients (76%) had diagnostic scans (see Table'I). Of those patients with nondiagnostic scans, 116 of the patients had scans demonstrating blood pooling and 55 patients had technically inadequate or unavailable scans. Of the 31 patients with unavailable scans, 30 patients were injected but not scanned and one patient was scanned but the subsequent image was unavailable.

The diagnostic accuracy of Imciromab Pentetate was based upon the results of images obtained 48 hours following injection. However, when 48-hour images were unavailable and 24-hour images were available, the final image assessment was based on the 24-hour result. For example, 33 of the 116 patients with persistence of radioactivity in the blood (blood pooling) had the interpretation formed on the basis of a 24-hour image results. In addition, of the 555 patients with diagnostic images, 21 patients had the final image interpretation formed on the basis of the 24-hour image result.

Blood pooling occurred in 54% of the 678 patients with available images at 24 hours and in 12.5% of the 664 patients with available images at 48 hours. For the 555 patients with diagnostic images, a median of 30.2 hours (minimum 2 hours) elapsed between the onset of chest pain and the administration of Indium In 111 Imciromab Pentetate. The mean administered dose of Indium In 111 Imciromab Pentetate was 2.1 ± 0.2 mCi (range: 1.0-3.8 mCi), and the mean percent incorporation of Indium In 111 was $96.6 \pm 2.5\%$ (range: 85.7-100%).

<p align="center">Table 1 DISTRIBUTION OF ALL PATIENTS ENROLLED BY IMAGE RESULTS AND BY FINAL CLINICAL DIAGNOSIS</p>						
IMAGE RESULTS		CLINICAL DIAGNOSIS				
		Total	AMI	Non-AMI		
				CP	UA	ND
Non-diagnostic images:	Blood pooling	116	47	9	59	1
	Technically inadequate	24	9	0	15	0
	Unavailable images	31	21	0	10	0
Sub-total		171	77	9	84	1
Diagnostic scans:	Positive (+) cardiac localization of Imciromab Pentetate	366	316	1	49	0
	Negative (-) cardiac localization of Imciromab Pentetate	189	62	33	94	0
Sub-total		555	378	34	143	0
GRAND TOTAL		726	455	43	227	1

AMI = definitive acute myocardial infarction; CP = definitive chest pain of other etiology; UA = definitive unstable angina pectoris; ND = nondefinitive diagnosis

Table 2 summarizes selected performance characteristics of Indium In 111 Imciromab Pentetate in the settings of AMI and unstable angina, both in the presence and absence of localization of Indium In 111 Imciromab Pentetate. Indium In 111 Imciromab Pentetate was most likely to detect AMI correctly in patients with anterior myocardial infarctions, Q-wave myocardial infarctions, or myocardial infarctions with elevated peak creatine kinase (CK) levels or elevated peak CK-MB levels. Indium In 111 Imciromab Pentetate localized to the heart in approximately one-third of the patients who were ultimately diagnosed with unstable angina. These data indicate that localization of Indium In 111 Imciromab Pentetate uptake in patients with unstable angina may possibly identify areas of myocardial necrosis not detectable by other means. Conversely, these findings may indicate that Indium In 111 Imciromab Pentetate sometimes localizes to ischemic, non-infarcted myocardial tissue (i.e., "false positive" localization).

Table 2
SELECTED PERFORMANCE CHARACTERISTICS OF INDIUM IN 111 IMCIROMAB PENTETATE BASED ON FINAL CLINICAL DIAGNOSIS AND FINAL IMAGE INTERPRETATION"

DEFINITIVE DIAGNOSIS	Estimate	95% Confidence interval
<u>Acute myocardial infarction</u>		
Positive (+) cardiac localization of Imciromab Pentetate ("sensitivity")		
• In patients with diagnostic images only	316/378 = 84%	(79%, 87%)
• In all patients imaged ^c	316/455 = 69%	(65%, 74%)
<u>Chest pain of other etiology</u>		
Negative (-) cardiac localization of Imciromab Pentetate ("specificity")		
• In patients with diagnostic images only ^c	33/34 = 97%	(85%, 100%)
<u>Unstable angina</u>		
Positive (+) cardiac localization of Imciromab Pentetate		
• In patients with diagnostic images only	49/143 = 34%	(27%, 43%)
• In all patients imaged ^b	49/227 = 22%	(16%, 28%)

"The data used in the calculations are from Table 1

^aAll imaged patients includes patients with diagnostic and non-diagnostic images

^cNine additional patients had non-diagnostic images

Indium In 111 Imciromab Pentetate uptake location (anterior, inferior, lateral, diffuse, indeterminate) was compared to the location of the infarct as assessed by the presence of a Q-wave (anterior, inferior, lateral) on the EKG.

Of the 455 patients with an AMI, 378 had diagnostic images that were either positive or negative for Indium In 111 Imciromab Pentetate localization. Of the 378 patients, 316 patients had an AMI and positive localization of Indium In 111 Imciromab Pentetate. Of these 316 patients with AMI and positive images, 185 had the presence of a Q wave on the EKG. In eight of these 185 patients, the location of the infarct could not be determined by the Q wave, leaving a total of 177 patients available for comparison of the EKG location to the Indium In 111 Imciromab Pentetate location. These 177 patients were utilized in the assessment of the diagnostic accuracy of Indium In 111 Imciromab Pentetate in the determination of the location of a myocardial infarction.

Of the 177 patients with a diagnostic image and an acute **Q-wave** myocardial infarction, the site of Indium In 111 Imciromab Pentetate localization agreed with EKG localization in 89% (95% CI: **84%**, 93%). The concordance for the various major locations of Q-wave myocardial infarction is shown in Table 3. For non-Q-wave myocardial infarctions, the site of Indium In 111 Imciromab Pentetate localization agreed with EKG localization (as assessed by ST-segment alterations) in 70% (23 of 33 patients).

Table 3
LOCALIZATION OF ACUTE Q-WAVE MYOCARDIAL INFARCTION: CONCORDANCE OF INFARCTS
LOCALIZED BY EKG WITH INDIUM In 111 IMCIROMAB PENTETATE LOCALIZATION

EKG Location	Indium In111 Imciromab Pentetate Image Result		
	Agreement/ Total number of positive EKGs	Concordance Estimate (%)	95% Confidence Interval (%)
Anterior MI	85/88	96.6	(90, 99)
Inferior MI	73/87	83.9	(74, 91)
Lateral MI	0/2	0	(0, 78)
Unknown MI	0/8	0	(0, 31)
Overall	158/185	85.4	(79, 90)

An estimation of the correlation of the extent of Indium In 111 Imciromab Pentetate cardiac localization with the size of the myocardial infarction was performed using an unblinded, retrospective analysis of image results and the subsequent clinical course of the patients. Of the 316 patients with positive images and a definitive diagnosis of AMI, the extent of Indium In 111 Imciromab Pentetate uptake (on each of the three imaging views) and follow-up clinical information were both obtained on 234 patients. In this subgroup, patients who had uptake of Indium In 111 Imciromab Pentetate in at least 10 of 18 cardiac segments (as compared to those with positive uptake in 1 to 9 segments) appeared to be at increased risk for subsequent cardiac death and non-fatal myocardial infarction.

C. Study C04I-005: The safety and diagnostic accuracy of delayed and repeated injections of Indium In 111 labeled antimyosin in ischemic heart disease

The primary objective of this supportive clinical study was to determine the sensitivity of Indium In 111 Imciromab Pentetate imaging in patients who experienced an MI at various times prior to performance of the imaging procedure. Additionally, certain patients also underwent repetitive Indium In 111 Imciromab Pentetate imaging procedures. This was a prospective study in which 48-hour Indium In 111 Imciromab Pentetate images were evaluated by a consensus of nuclear cardiologists blinded to the clinical information.

Results

As shown in Table 4, the proportion of patients with positive Indium In 111 Imciromab Pentetate images declined in the subgroups of patients with increasing time intervals between the initial MI and the imaging procedure. There was a statistically significant decrease in the sensitivity over time ($p < 0.001$, logistic regression).

Table 4
NUMBER (%) OF PATIENTS WITH AND WITHOUT LOCALIZATION OF INDIUM In 111 IMCIROMAB
PENTETATE AFTER A PRIOR MYOCARDIAL INFARCTION

Time (months) from AMI to initial injection of Indium In 111 Imciromab Pentetate					
	<u>0-2</u>	<u>2-4</u>	<u>4-6</u>	<u>6-8</u>	<u>8-10</u>
<u>Imaae Results</u>					
Positive	51 (72%)	23 (70%)	9 (53%)	18 (45%)	3 (23%)
Negative	20 (28%)	10 (30%)	8 (47%)	22 (55%)	10 (76%)

Subgroup analyses of the proportion of positive images showed no significant difference in the estimated rate of decrease in proportion over time for Q-wave versus non-Q wave myocardial infarcts ($P = 0.499$), for anterior versus inferior/lateral infarcts ($p = 0.868$), for a peak CK level $\leq 2,000$ versus ≥ 2000 U/L ($p = 0.238$) or for patients who did or did not receive thrombolytic therapy for the initial MI ($p = 0.799$). The five latest positive images were obtained 415, 370, 304, 302 and 293 days post MI. No positive images were seen when the initial injection was made more than fourteen months after the MI ($n = 8$). The latest any patient was injected was 474 days post MI (and the resulting image was negative).

A similar decrease in the proportion of positive images was noted when repeat injections were compared to first injections. These data indicate that Indium In 111 Imciromab Pentetate localized to the heart in a substantial proportion of patients, even when the injections were made months after the acute myocardial infarction. The interpretation of a positive Indium In 111 Imciromab Pentetate image may therefore be influenced by prior myocardial infarctions. Repeat injections in this study did not increase the rate of non-diagnostic imaging studies, suggesting that repeat Indium In 111 Imciromab Pentetate studies may be performed.

Of the 185 patients enrolled, 132 (71%) received one injection, 40 (22%) received two injections, 10 (5%) received three injections, and 3 (2%) received five injections. None of the patients with evaluable samples had human antimurine antibody (HAMA) responses following single or repeat injections,

D. Safety profile

Safety data were evaluated in 1,318 human subjects who received 1,394 injections of Indium In 111 Imciromab Pentetate. These data include all the patients who participated in the 10 Centocor sponsored clinical trials. 1,261 patients received a single injection and 57 patients received 2 to 5 injections. The patients enrolled in the clinical protocols may be grouped into those involving:

- acute ischemic heart disease (IHD) n = 1,113
- stable coronary artery disease (CAD) n = 120
- chest pain of other etiology n = 43
- other (nonischemic) diagnoses n = 42

The mean administered dose for all 1318 first injections was 2.1 ± 0.2 mCi. No studies were performed in children.

Patients experiencing adverse events are summarized in Table 5.

Table 5
PATIENTS WITH ADVERSE EVENTS BY RELATIONSHIP, SERIOUSNESS, INTENSITY

	<u>Acute IHD</u>	<u>Stable CAD</u>	<u>Chest pain</u>	<u>Other</u>	<u>Total</u>
Patients injected	1113 (100%)	120 (100%)	43 (100%)	42 (1 00%)	1318
Patients with adverse events	453 (41%)	9 (7.5%)	12 (28%)	6 (14%)	480 (36%)
Relationship					
Definitely related	1 (0.1%)	0	0	0	1 (0.1%)
Probably related	10 (0.9%)	0	0	0	10 (0.8%)
Possibly related	19 (1.7%)	2 (1.7%)	1 (2.3%)	0	22 (1.7%)
Probably not related	262 (23.5%)	6 (5%)	8 (19%)	1 (2.4%)	277 (21%)
Definitely not related	160 (14%)	1 (0.8%)	3 (7%)	5 (12%)	169 (13%)
Missing relation	1 (0.1%)	0	0	0	1 (0.1%)
Serious Adverse Events					
Yes	79 (7.1%)	0	0	3 (7.1%)	82 (6.2%)
No	374 (33.6%)	9 (7.5%)	12 (27.9%)	3 (7.1%)	398 (30.2%)
Intensity					
Severe	91 (8.2%)	1 (0.8%)	1 (2.3%)	1 (2.4%)	94 (7.1%)
Moderate	150 (13.5%)	1 (0.8%)	5 (11.6%)	1 (2.4%)	157 (11.9%)
Mild	210 (18.9%)	7 (5.8%)	6 (14%)	1 (2.4%)	224 (17%)
Missing	2 (0.2%)	0	0	3 (7.1%)	5 (0.4%)

Almost all patients with adverse events that were judged to be associated with Indium In 111 Imciromab Pentetate also had acute ischemic heart disease. Adverse events that occurred in $\geq 0.5\%$ of the 1,318 patients that were felt to be definitely, probably, or possibly related to Indium In 111 Imciromab Pentetate included injection site pain (0.8%) and fever (0.6%). Administration of Indium In Imciromab Pentetate was not discontinued in any patient due to an adverse event.

No anaphylaxis or hypersensitivity reactions were reported. None of the 45 patient deaths or 150 serious adverse events were reported by the investigators as definitely or probably related to Indium In 111 Imciromab Pentetate. One death that occurred in a patient with a prior cardiac arrest and ventricular failure was judged to be possibly related to Indium In 111 Imciromab Pentetate. After injection, this patient experienced hypotension (possibly related) and a cardiac arrest (probably not related) and died 10 minutes after the injection. Serious adverse events reported as possibly related were infrequent. Three of these events (delirium, confusion and hypotension) occurred in one patient.

Among the 1,318 evaluable patients, 480 patients experienced a total of 1,271 adverse events (see Table 6). One patient experienced two adverse events of mild intensity (dry mouth, sweet taste) that were felt to be definitely related to Indium In 111 Imciromab Pentetate.

Table 6
PATIENTS EXPERIENCING ADVERSE EVENTS

	Acute IHD	Stable CAD	Chest Pain	Other	Total
Patients injected (n)	1113	120	43	42	1318
Patients reporting (n, % within the diagnostic category):					
Chest pain	159 (14%)	1 (0.8%)	5 (12%)	0	165 (13%)
Fever	118 (11%)	0	1 (2.3%)	0	119 (9%)
Headache	83 (8%)	1 (0.8%)	7 (16%)	0	91 (7%)
Nausea	59 (5%)	0	3 (7%)	1 (2%)	63 (5%)
Pain	59 (5%)	1 (0.8%)	1 (2.3%)	1 (2.4%)	62 (4.7%)
Dyspnea	37 (3%)	0	0	2 (5%)	39 (3%)
Vomiting	31 (3%)	0	2 (5%)	1 (2%)	34 (2.6%)
Back pain	28 (2.5%)	1 (0.8%)	2 (4.7%)	0	31 (2.4%)
Hypotension	28 (2.5%)	2 (1.7%)	0	0	30 (2.3%)
Abdominal pain	28 (2.5%)	0	1 (2.3%)	0	29 (2.2%)
Dizziness	23 (2.1 %)	0	2 (4.7%)	0	25 (1.9%)
Angina Pectoris	25 (2.2%)	0	0	0	25 (1.9%)
Dyspnea	16 (1.4%)	0	1 (2.3%)	0	17 (1.3%)
Diaphoresis	16 (1.4%)	0	0	0	16 (1.2%)
Cardiac arrest	15 (1.3%)	0	0	1 (2%)	16 (1.2%)
Tachycardia, (Vent)	15 (1.3%)	0	0	0	15 (1.1%)
Heart failure	15 (1.3%)	0	0	0	15 (1.1%)
Injection site pain	14 (1.3%)	0	0	0	14 (1.1%)
Rash	12 (1.1%)	0	1 (2%)	0	13 (1%)
Confusion	13 (1.2%)	0	0	0	13 (1%)
Constipation	13 (1.2%)	0	0	0	13 (1%)

Of 53 patients who received multiple injections of Indium In 111 Imciromab Pentetate (up to five times) four patients reported adverse events following repeat injection (chest pain, headache, nausea, fatigue), all of which were considered definitely not or probably not related to the study agent.

There were 914 patients with serum samples evaluable for human antimurine antibody (HAMA) responses to Indium In 111 Imciromab Pentetate injection. The mean time to sampling post-injection was 23.3 ± 14.7 days. One patient had a low-level titer HAMA response. None of the other patients had HAMA responses, including 53 patients injected up to five times.

The maximum amount of Imciromab Pentetate that can safely be administered has not been determined. The maximal recommended intravenous dose of Indium In 111 in a single dose is 2.2 mCi (81 MBq).

The estimated absorbed radiation doses, at the time of Indium In 111 expiration to an adult patient weighing 70 kilograms, from an intravenous dose of 2 mCi (74 MBq) of Indium In 111 Imciromab Pentetate, including maximal contributions from Indium 114m/114 as radionuclide impurity, are shown in Table 7. The radionuclide impurity limit for Indium 114m/114 is not greater than 0.16% at the time of expiration. The effective dose equivalent (EDE) for 2 mCi Indium In 111 Imciromab Pentetate is 1.92 rem (19.2 mSv), which includes 0.3 rem (3.0 mSv) from maximal impurity levels (0.16% of Indium In 111 m/l 14).

Table 7
RADIATION DOSIMETRY

Tissue	Rad / 2 mCi	mGy 174 MBq
Kidneys	8.8	88
Liver	4.5	45
Spleen	3.4	34
Red marrow	3.2	32
Heart wall ^a	1.5	15
Bladder wall ^b	1.4	14
Lung	1.4	14
Bone	1.0	10
Small intestine	0.9	9
Ovaries	0.8	8
Uterus	0.8	8
Testes	0.4	4
Thyroid	0.4	4
Total body	0.8	8

^aHeart wall and heart chamber contents were source terms

^bBladder content was the source term and assumes five urinary voids per day

VI. ADVISORY COMMITTEE REVIEW

The clinical data were reviewed by the 77th meeting of the Cardiovascular and Renal Drugs Advisory Committee on January 26, 1996. The committee voted to recommend approval for the indication of detection of myocardial infarction.

VII. APPROVED PACKAGE INSERT

A copy of the approved package insert is attached

Appendix A

SUMMARY OF TEST AND SPECIFICATIONS FOR ANTIMYOSIN FAB-DTPA

FERMENTATION SAMPLES (within 7 days of inoculation and at the end of fermentation)

Test	Test Method	Specification
Mycoplasma Cultivable Non-cultivable	(b)(4)	No mycoplasma detected No mycoplasma detected
Retrovirus Testing' Dunni Cell Assay, direct		$\leq 10^2$ sfu/ml

FERMENTATION SAMPLES AT THE END OF FERMENTATION

Test	Test Method	Specification
<i>In vitro</i> test for adventitious viruses on:	Tektagen or Microbiological Associates	
Vero cells		No virus detected
MRC-5 cells		No virus detected
HeLa cells		No virus detected
C4 cells		No virus detected

ANION EXCHANGE PURIFIED ANTIMYOSIN Fab

Test	Test Method	Specification
DNA content	(b)(4)	≤ 20 pg/mg

MODIFICATION OF ANTIMYOSIN Fab BY DTPA ANHYDRIDE

Test	Test Method	Specification
DTPA/Fab determination by In-l 11 incorporation	(b)(4)	1.25 -2.25 DTPA per Fab


¹ A sample taken at the end of fermentation from the first five fermenters from each new WCB will be tested for ERV by the Dunni Cell assay. If the results are negative, testing of fermenters will stop. If the results are positive, all fermenters will be tested for ERV. All preformulated bulks from fermenters that are positive for ERV must be tested and found negative by the extended Dunni Cell assay.

Appendix B

SUMMARY OF TEST AND SPECIFICATIONS FOR ANTIMYOSIN Fab-DTPA






PREFORMULATED BULK

(If the fermenter is positive for a retrovirus, i.e. I-I 00 sfu/ml)


Test	Test Method	Specification
Retrovirus testing: Dunni Cell assay, extended		No virus detected

(b)(4)

FINAL BULK

Test	Test Method	Specification
Sterility		No growth
PH		6.4 to 6.6
Protein concentration by OD,,		0.45 to 0.55 mg/ml
Identity by IEF		Conforms to standard
In-I 11 incorporation by citrate ITLC		≥ 90% within 10 minutes

FINAL BULK 0.2 M CITRATE pH 5.0













Test	Test Method	Specification
Sterility		No growth

(b)(4)

Appendix C

SUMMARY OF TEST AND SPECIFICATIONS FOR ANTIMYOSIN Fab-DTPA

FINAL CONTAINER

Test		Test Method	Specification
Color			Colorless
Appearance			Clear liquid
pH	(b)(4)		6.4 to 6.6
Particles			Free of foreign particles; Essentially free of proteinaceous particles, conforms to Picture A or B
Fill volume			range: 1.05 to 1.20 mL mean: ≥ 1.10 mL
Protein concentration by OD ₂₈₀			0.45 to 0.55 mg/mL
Purii and identity by GF-HPLC	(b)(4)		$\geq 98\%$ as main component; RT \pm 0.1 minutes between standard and sample
Purii of Fab-DTPA by SDS-PAGE (Non-reduced)			$\geq 97\%$ purity
Charge distribution by IEF			Conforms to Reference Standard Region B = 0.8 - 1.2 of Reference Standard; Region A = $\leq 10\%$ and Region C = 5 - 35%
In-I 11 incorporation ¹ by citrate and WEAITLC	(b)(4)		$\geq 90\%$ within 10 minutes
Immunoreactive fraction by myosin affinity column ¹			$\geq 84\%$ [$\geq 90\%$] ²
Endotoxin ¹			≤ 20 EU/mg
Sterility ¹		21CFR 610.12	No growth
General Safety ¹		21 CFR 610.11	Non-toxic







¹ Assays are performed with the designated lot of 0.2 M citrate pH 5.0 (Vial 2)

² Brackets indicate initial release specification

Appendix C (continued)

SUMMARY OF TEST AND SPECIFICATIONS FOR ANTIMYOSIN Fab-DTPA

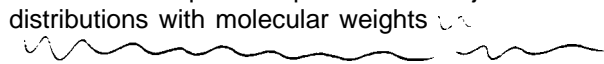

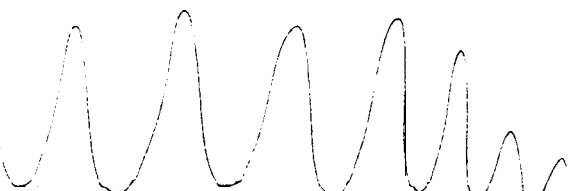
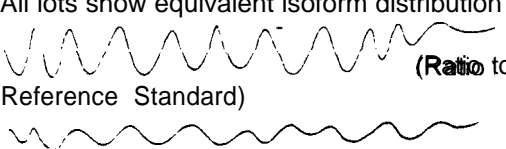
FINAL CONTAINER 0.2 M CITRATE pH 5.0

Test	Test Method	Specification
Color		Colorless
Appearance		Clear liquid
pH	(b)(4) 	4.9 - 5.1
Particles		Free from foreign particles
Fill volume		range: 0.90 to 1.10 mL mean: 0.95 to 1.05 mL
Assay citrate	BP	180 to 220 mM
Endotoxin by LAL ¹		≤ 20 EU/mL
Sterility'	21CFR 610.12	No growth
General safety'	21 CFR 610.11	Non-toxic
In-l 11 incorporation'	SOP 41A	≥ 90% within 10 minutes

¹ Assays are performed with the designated lot of antimyosin Fab-DTPA (Vial 1)

APPENDIX D

SUMMARY OF ANTIMYOSIN Fab-DTPA¹ PRODUCT EQUIVALENCE STUDIES FOR FIVE CONSECUTIVE DSP LOTS

Analysis	Result (Mean \pm S.D. ²)
BIOCHEMICAL AND BIOPHYSICAL	
Fab molecular weight by mass spectrometry	All lots show equivalent pattern of 4 major distributions with molecular weights consistent with multiple glycoforms.
(b)(4)	
N-terminal amino acid sequence by automated Edman degradation	All lots show identical dual (Fd,L) sequence:
(b)(4)	
Fab tryptic peptide map by HPLC	All lots show superimposable maps
Monosaccharide composition analysis	All lots show equivalent monosaccharide composition:
(b)(4)	
Molecular conformation by circular dichroism	All lots show equivalent spectra with near UV minima of 262,269 and 277 nm, and a maximum of 292 nm, while far UV has a 216 nm minimum
Molecular size by GF-HPLC	All lots show consistent profiles, 100% Fab-DTPA
Purity by SDS-PAGE	All lots equivalent, mean purity $98.9 \pm 0.3\%$ Fab-DTPA
Size and composition by SDS-PAGE	All lots show consistent supunit profiles and minor band distributions
Charge microheterogeneity by IEF	All lots show equivalent isoform distribution
(b)(4)	
DTPA per Fab	All lots equivalent, 1.52 ± 0.09 DTPA per Fab

APPENDIX D (continued)

SUMMARY OF ANTIMYOSIN Fab-DTPA¹ PRODUCT EQUIVALENCE STUDIES FOR
FIVE CONSECUTIVE DSP LOTS

RADIOCHEMICAL AND IMMUNOCHEMICAL

In-I 11 incorporation	All lots equivalent, $96 \pm 1\%$ mean incorporation by citrate ITLC and $98 \pm 1\%$ by WEAITLC
Immunoreactive fraction	All lots equivalent, $95 \pm 3\%$ mean immunoreactive fraction

¹ Certain tests performed on antimyosin Fab as indicated

² Where applicable

APPENDIX E

PROCESS VALIDATION SUMMARY: REMOVAL OF SPECIFIC CONTAMINANTS (Level in PFB)

Contaminant	Concentration as Determined by Direct Measurement	Reduction Calculated from Testing Process Intermediates of Spike Study
Bovine Serum Albumin (BSA)	< 4.3 ng per dose	> 7.0 logs (endogenous BSA)
Bovine IgG	< 8.0 to 60 ng per dose	3.4 - 4.5 logs (endogenous BlgG)
IgG1	< 250 ng per dose	NA
Host cell DNA	< 10 pg per dose	> 8.1 logs (endogenous DNA)
Gentamicin	< 0.5 ug per dose	> 2.6 -> 2.7 logs (endogenous gentamicin)
Papain	0.1 - 0.5 ng per dose	4.2 - 4.3 logs (endogenous papain)
Iodoacetamide (IAM)	NA	5.8 logs (spike study)
Guanidine	< 1.3 ug per dose	5.2 logs (spike study) > 2.4 logs (endogenous guanidine)
Protein A	< 0.6 ng per dose	>0.8 ->2.2 logs (endogenous Protein A)
Endotoxin	under control	NA
Bioburden	under control	NA
Trace metals	under control	NA
Chelex leachables	undetectable	NA
Virus	undetectable	≥ 15.2 logs for MuLV ≥ 10.4 logs for SV-40 6.1 logs for Poliovirus Type I

NA = Not Available

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20 Feb 1997

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March 26, 1997

Date

3/7/97

Date

Feb 24, 1997

Date

March 7, 1997

Date

Feb 25, 1997

Date

June 19 1997

Date

March 7, 1997

Date

3/7/97

Date